Reduced ^{123}I-BMIPP uptake implies decreased myocardial flow reserve in patients with chronic stable angina

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Abstract

Long-chain fatty acid (LCFA) is the main energy source for normal myocardium at rest. In ischemic myocardium, the main energy substrate shifts from LCFA to glucose. ^{123}I-BMIPP is a radiolabeled LCFA analogue. In chronic stable angina without previous infarction, we suppose that reduced ^{123}I-BMIPP uptake is related to the substrate shift in myocardium with decreased myocardial flow reserve (MFR).

Methods: We enrolled 21 patients with chronic stable angina without previous infarction who underwent ^{123}I-BMIPP single photon emission tomography (SPECT) and ^{15}O-labeled water positron emission tomography (PET). The left ventricle was divided into 13 segments. In each segment, rest myocardial blood flow (MBF) and hyperemic MBF were measured by PET. ^{123}I-BMIPP uptake was evaluated as follows (^{123}I-BMIPP score 0 = normal; 1-3 = low uptake; 4= complete defect). ^{123}I-BMIPP uptake was compared with rest MBF, hyperemic MBF and MFR.

Results: The numbers of segments with ^{123}I-BMIPP scores 0 to 4 were 178, 40, 25, 24 and 0, respectively. The rest MBFs of scores 0 to 3 were 0.93±0.25, 0.86±0.21, 0.97±0.30 and 0.99±0.37 ml/min/g, respectively. The hyperemic MBFs of scores 0 to 3 were 2.76±1.29, 1.84±0.74, 1.37±0.39 and 1.08±0.40 ml/min/g, respectively. The MFRs of scores 0 to 3 were 3.01±1.38, 2.20±0.95, 1.44±0.22 and 1.10±0.26, respectively. As ^{123}I-BMIPP uptake reduced,

hyperemic MBF and MFR decreased.

Conclusion: In chronic stable angina without previous infarction, reduced ^{123}I-BMIPP uptake implies decreased MFR.

Key words:

^{123}I-BMIPP

Myocardial flow reserve

Substrate shift

Long-chain fatty acid metabolism

Footnotes: ^{123}I-BMIPP versus myocardial flow reserve

Introduction

Long-chain fatty acid (LCFA) is the main energy source for normal myocardium at rest [1-3]. Reduced LCFA metabolism was reported both experimentally and clinically in ischemic myocardium [4-6]. In ischemic myocardium, the main energy substrate shifts from LCFA to glucose [7-14].

^{123}I-BMIPP is a radiolabeled LCFA analogue and is commercially available in Japan. Reduced ^{123}I-BMIPP uptake has been reported in patients with ischemic heart disease [15-24]. In the diagnosis of chronic stable angina, stress myocardial perfusion scintigraphy is superior to ^{123}I-BMIPP scintigraphy [25]. In the prediction of prognosis, previous studies suggested that ^{123}I-BMIPP was useful to predict functional recovery of myocardium [21, 26].

In chronic stable angina, myocardial flow reserve (MFR) is decreased [27]. Decreased MFR causes myocardial ischemia when the demand of myocardial blood flow (MBF) exceeds its maximum supply. As MRF is decreased, myocardium is more susceptible to ischemia and more repeatedly exposed to ischemia [10]. The relation between 123I-BMIPP uptake and the severity of repeated ischemic episodes, however, has not yet been demonstrated.

We suppose that reduced ^{123}I-BMIPP uptake is suggestive of the severity of

ischemic episodes. In this study, ^{123}I-BMIPP uptake was compared with rest myocardial blood flow (MBF), hyperemic MBF and MFR assessed with ^{15}O-water positron emission tomography (PET). We investigated the relation of ^{123}I-BMIPP uptake to rest MBF, hyperemic MBF and MFR.

Materials and Methods

Study population

We enrolled 21 patients with chronic stable angina without previous infarction. The details of the patients are shown in Table 1. In all patients, coronary angiography (CAG) was performed and coronary artery disease (CAD) was identified. Significant coronary stenosis was defined as ≧ 90% by visual assessment. In this study, we regarded the condition of patients as chronic stable angina when no evident attack has been observed for more than 2 weeks until ^{123}I-BMIPP-SPECT or ^{15}O-water PET.

Protocol

^{123}I-BMIPP SPECT and ^{15}O-water PET were performed within 1 week.

^{123}I-BMIPP-SPECT

^{123}I-BMIPP is commercially available in Japan (Nihon Medi-Physics Co., Ltd., Hyogo, Japan). After the patients fasted for 3 hours, ^{123}I-BMIPP (111 MBq) was injected into the patients while they are at rest. SPECT was initiated (ADAC Vertex, ADAC

Laboratories, Milpitas, CA, USA) 30 minutes after the injection. The energy discrimination was centered on 159 keV with a 20% window. A low-energy high-resolution collimator was used. The data were acquired in a 64 × 64 matrix. Thirty-two projection images were acquired over 180°, 60 seconds per step. The projection data were prefiltered with a two-dimensional Butterworth filter and reconstructed with filtered back-projection without attenuation correction. The spatial resolution was approximately 12 mm full-width at half-maximum (FWHM) after reconstruction [28, 29].

^{15}O-water PET

All patients refrained from drinking caffeinated beverages for at least 24 hours before PET [30, 31].

Rest MBF and adenosine-induced hyperemic MBF were quantified by ^{15}O-water PET. The PET scanner was ECAT EXACT HR+ (Siemens/CTI). A 6-minute transmission scan with a rotating rod source of ^{68}Ge (a positron emitter) was performed to correct photon attenuation. ^{15}O-labeled carbon monoxide (^{15}O-CO) was inhaled for 1 minute. The total dose of ^{15}O-CO was 2000 MBq. After a 3-minute interval to combine ^{15}O-CO with hemoglobin, a 5-minute blood volume scan was performed. After a 5-minute interval for the decay of radioactivity, 1500 MBq ^{15}O-water was infused into

an antecubital vein, and the first 6-minute dynamic PET of 24 frames was started to quantify rest MBF. After a 6-minute interval, a slow adenosine infusion for 9 minutes at the rate of 0.16 mg/kg/min was initiated. The second dynamic scan of 24 frames for hyperemic MBF was started 3 minutes later [28, 32, 33].

Calculation of MBF and MFR

Rest MBF and hyperemic MBF and MFR were calculated by a program developed by Katoh et al [28, 32, 33]. In brief, the program automatically divides the left ventricular wall into 13 regions of interest (ROIs) as shown in Figure 1. The ROIs consisted of 6 segments each of the basal and apical left ventricular wall and one segment of the apex. The program automatically calculates rest and hyperemic MBF and MFR of each ROI and displays these parameters and the color polar maps of these parameters.

^{123}I-BMIPP score

The left ventricular wall was divided into 13 segments corresponding to the ROIs of ^{15}O-water PET. ^{123}I-BMIPP uptake was scored in each segment with a visual five-grade scale (0: normal; 1: slightly decreased uptake; 2: moderately decreased uptake; 3: severely decreased uptake; 4: complete defect). Two skillful nuclear cardiologists independently scored ^{123}I-BMIPP uptake. Disagreements in the scores

were resolved through discussion and the number of segments of each ^{123}I-BMIPP score was finally concluded.

Data analysis

The agreement (kappa) between the two observers on the ^{123}I-BMIPP scores was measured. A weighted kappa was also measured to evaluate the interobserver variability. The weight was set at the difference of the scores between the two observers.

Rest MBF and hyperemic MBF and MFR of the segments of each score were averaged. The standard deviation of each parameter was calculated. Rest MBF of each score was compared with each other. Hyperemic MBF and MFR were compared similarly. Statistical comparison was performed using the Scheffe multiple comparison test ($p<0.05$).

Results

Patients backgrounds are shown in Table 1. Our study population consisted of 15 males and 6 females. The average age was 64.5±11.8 (Mean±SD) years. The average height and weight were 160.7±8.4 cm and 60.4±10.0 kg, respectively. Table 1 includes percent stenosis of each coronary artery and cardiovascular risk factors in each patient.

The averages and standard deviations of the mean blood pressure at rest and

during adenosine infusion were 99.0±8.8 and 84.4±10.1 (mmHg), respectively ($p<0.0001$). The averages and standard deviations of the heart rate at rest and during adenosine infusion were 68.3±9.6 and 81.0±6.9 (beats/min), respectively ($p<0.0001$). The averages and standard deviations of the rate pressure product at rest and during adenosine infusion were 6776.1±1201.4 and 6864.1±1123.0 (mmHg/min), respectively (p=ns).

The results of ^{123}I-BMIPP uptake from the two observers are shown in Table 2. The kappa was 0.68. The weighted kappa was 0.81.

The images of a 60-year-old woman with significant coronary stenosis (left anterior descending (LAD) 90%, circumflex (Cx) coronary artery 99%) are shown in Figure 2. ^{123}I-BMIPP uptake almost parallels hyperemic MBF and MFR.

The conclusive numbers of segments of each ^{123}I-BMIPP score are shown in Table 3. The numbers of segments with ^{123}I-BMIPP scores 0 to 4 were 178, 40, 25, 24 and 0, respectively. Rest and hyperemic MBF and MFR of ^{123}I-BMIPP scores 0 to 3 were compared.

The rest MBFs of scores 0 to 3 was 0.93±0.25, 0.86±0.21, 0.97±0.30 and 0.99±0.37 ml/min/g, respectively (Figure 3a). The hyperemic MBFs of scores 0 to 3 were 2.76±1.29, 1.84±0.74, 1.37±0.39 and 1.08±0.40 ml/min/g, respectively (Figure 3b). The

MFRs of scores 0 to 3 were 3.01±1.38, 2.20±0.95, 1.44±0.22 and 1.10±0.26, respectively (Figure 3c).

Discussion

These results suggested that as ^{123}I-BMIPP uptake decreased, hyperemic MBF and MFR decreased and that definitively reduced ^{123}I-BMIPP uptake (score 2 and 3) indicated markedly decreased MFR.

The supply and demand of MBF is balanced through MFR in chronic stable angina. The increased demand beyond the adjustable range of MFR results in myocardial ischemia. In ischemic condition, both substrate and oxygen are insufficient. In such condition, oxygen insufficiency precedes substrate insufficiency in all tissue including myocardium. In other words, myocardial ischemia is regarded as relative hypoxia.

Hypoxia inhibits the activity of peroxisome proliferator-activated receptor-alpha (PPARα). Carnitine palmitoyltransferase 1 (CPT-1), the rate-limiting enzyme for LCFA oxidation in mitochondria, and mitochondrial fatty acid β-oxidation (FAO) are regulated by PPARα [34, 35]. Repetitive hypoxia due to reduced MFR possibly decreases the activity of PPARα. As a result, CPT-1 and FAO are inhibited and LCFA

metabolism is suppressed. In fact, basic research suggested that repetitive ischemia caused the substrate shift from LCFA to glucose [11].

^{123}I-BMIPP is considered to indicate the activity of myocardial LCFA metabolism [36-38]. ^{123}I-BMIPP is incorporated into cardiomyocytes. It is associated with CD36 [37-39], and fatty acid binding protein [36]. ^{123}I-BMIPP and natural LCFAs share the metabolic pathway.

The metabolism of ^{123}I-BMIPP is different from that of natural LCFAs. The methyl branch prolongs the retention of ^{123}I-BMIPP in the cytoplasm [40, 41]. ^{123}I-BMIPP is rapidly extracted and mainly retained in the triglyceride pool (TG pool). A small fraction of nonmetabolized ^{123}I-BMIPP and its metabolites is washed out from the myocardium [42].

The increasing severity of myocardial ischemia enhances the back-diffusion of ^{123}I-BMIPP to blood. The back-diffusion is also enhanced by the administration of etomoxir, a specific inhibitor of CPT-1 [43, 44].

Nielsen et al. reported that TG pool , the main reservoir for ^{123}I-BMIPP and natural LCFAs, was downscaled in myocardium of the patients who underwent coronary artery bypass graft. They indicated that hypoxia was related to the overexpression of microsomal triglyceride transfer protein, which led to the reduction of

TG pool [45].

In summary, reduced ^{123}I-BMIPP uptake due to decreased MFR is probably related to repetitive hypoxia. Our results suggested that definitively reduced ^{123}I-BMIPP uptake indicated reduced LCFA metabolism in myocardium with decreased MFR.

In effort angina, exogenous glucose uptake is increased after exercise-induced ischemia [12]. Repeated ischemia prolongs abnormal wall motion and the substrate shift from LCFA to glucose. Subsequently, myocardium exposed to repeated ischemia is adapted to chronic ischemia. This adaptation is called hibernation, where the main energy substrate shift from LCA to glucose, contractility is impaired, and MFR is severely reduced [9, 11, 13, 14]. Our study possibly suggests that the substrate shift in hibernation.

Animal experiment on myocardial metabolism due to chronic stable angina is probably difficult, because chronic stable angina is caused by long-term progressive coronary stenosis. Conversely, clinical studies are suitable for research on myocardial metabolism.

No method to quantify ^{123}I-BMIPP uptake has been established. The best approach would have been normalization of ^{123}I-BMIPP uptake for its maximum. Visual

assessment was unavoidable because attenuation correction could not be available for SPECT, and breast attenuation and diaphragmatic attenuation underestimate ^{123}I-BMIPP uptake.

Another limitation of this study is the fact that we enrolled 20 patients who had one or more cardiovascular risk factors. These risk factors may impair MFR due to microangiopathy [46-49]. SPECT only provides a relative display of tracer uptake. In addition, the ^{123}I-BMIPP scores were based on subjective estimation and, therefore, differed to some degree between two observers. However, the interobserver agreement was satisfactory in a pertinent statistical analysis.

Conclusion

In chronic stable angina without previous infarction, reduced ^{123}I-BMIPP uptake implies decreased MFR. This might be explained by reduced LCFA metabolism in myocardium with decreased MFR.

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Table 1

Patients backgrounds

Age (y.o.)	Gender (M/F)	Height (cm)	Weight (kg)	LAD	Cx	RCA	HT	HL	DM	Smoking
72	M	157	54	90%						+
68	M	160	65			99%	+	+		+
42	M	161	56		99%		+	+	+	+
79	M	159	47		99%	90%	+	+		+
73	M	162	62	90%	90%	90%	+		+	+
68	M	172	71	90%	99%	90%	+		+	+
48	M	171	72	90%	90%		+	+		+
74	M	166	60	90%			+	+		+
69	M	160	62	90%	100%		+			+
46	M	172	78	90%				+		+
75	M	164	55	90%			+			+
85	M	163	60	90%	90%	90%	+	+		
75	M	164	68			90%	+	+	+	+
67	M	166	56	90%		90%		+		+
57	M	164	73	100%				+		+
68	F	143	40	90%	90%		+		+	
73	F	149	53	90%	90%	90%		+	+	
63	F	152	73	90%						
44	F	152	53	90%	90%		+	+	+	
60	F	152	47	90%	99%			+		+
69	F	148	49	90%				+		+

Abbreviations: Left anterior descending (LAD) Artery, circumflex (Cx) coronary artery, right coronary artery (RCA), HT (Hypertension), HL (hyperlipidemia), DM (diabetes mellitus).

Table 2

Inter-observer agreement

		Observer 2					
	score	0	1	2	3	4	
Observer 1	0	150	15	0	0	0	165
	1	10	30	7	0	0	47
	2	0	8	20	4	0	32
	3	0	0	5	18	0	23
	4	0	0	0	0	0	0
		160	53	32	22	0	267

The kappa was 0.68. The weighted kappa was 0.81.

Table 3

^{123}I-BMIPP score vs. Rest and hyperemic MBF and MFR.

^{123}I-BMIPP score	Number of segments	Rest MBF (ml/min/g)	Hyperemic MBF (ml/min/g)	MFR
0	178	0.93±0.25	2.76±1.29	3.01±1.38
1	40	0.86±0.21	1.84±0.74	2.20±0.95
2	25	0.97±0.30	1.37±0.39	1.44±0.22
3	24	0.99±0.37	1.08±0.40	1.10±0.26
4	0	–	–	–

The average and standard deviation of rest and hyperemic MBF and MFR of each score are shown.

Figure 1

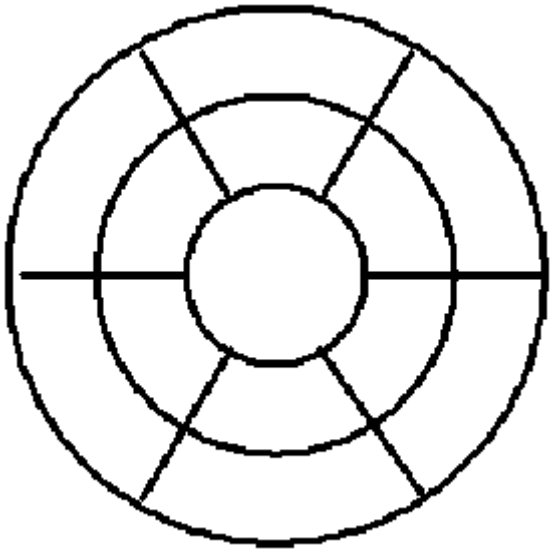

Figure 2

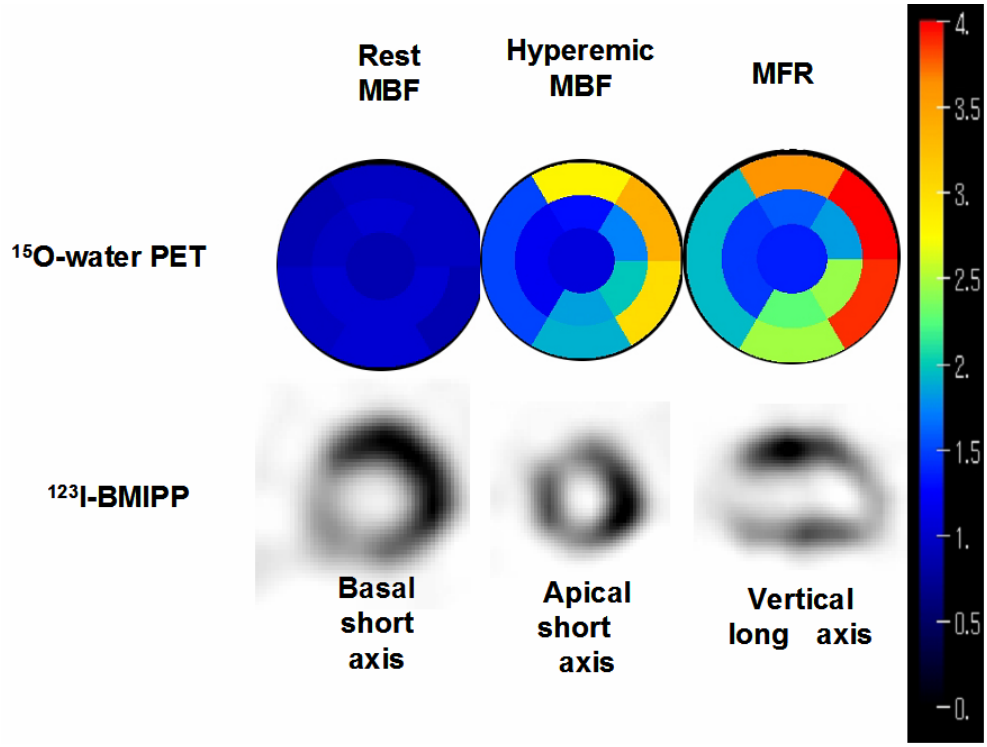
Rest MBF
Hyperemic MBF
MFR
15O-water PET
123I-BMIPP
4.
3.5
3.
2.5
2.
1.5
1.
0.5
0.
Basal short axis
Apical short axis
Vertical long axis

Figure 3a

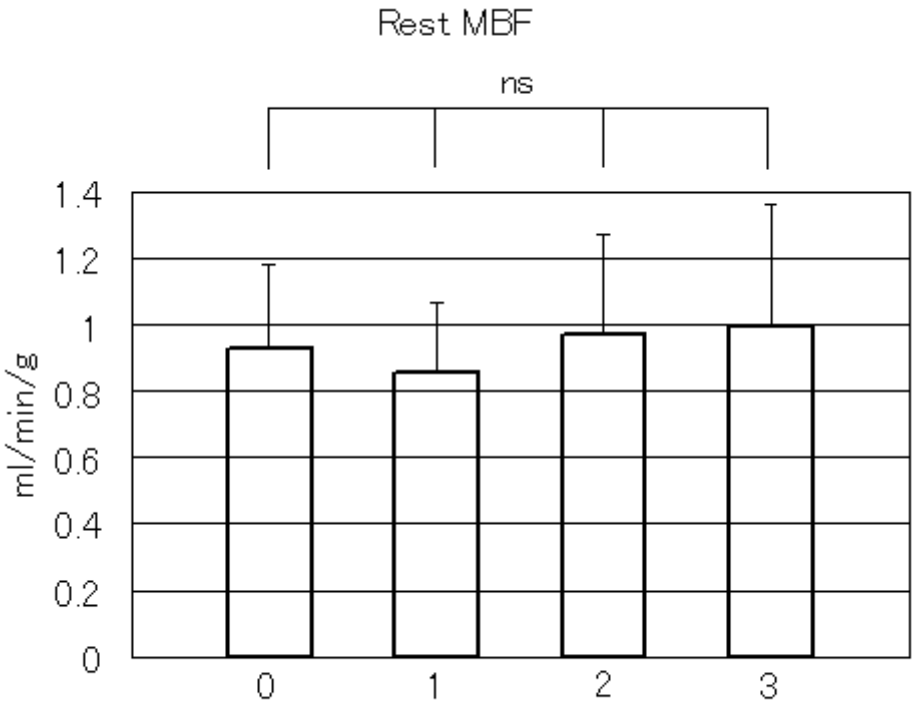

Figure 3b

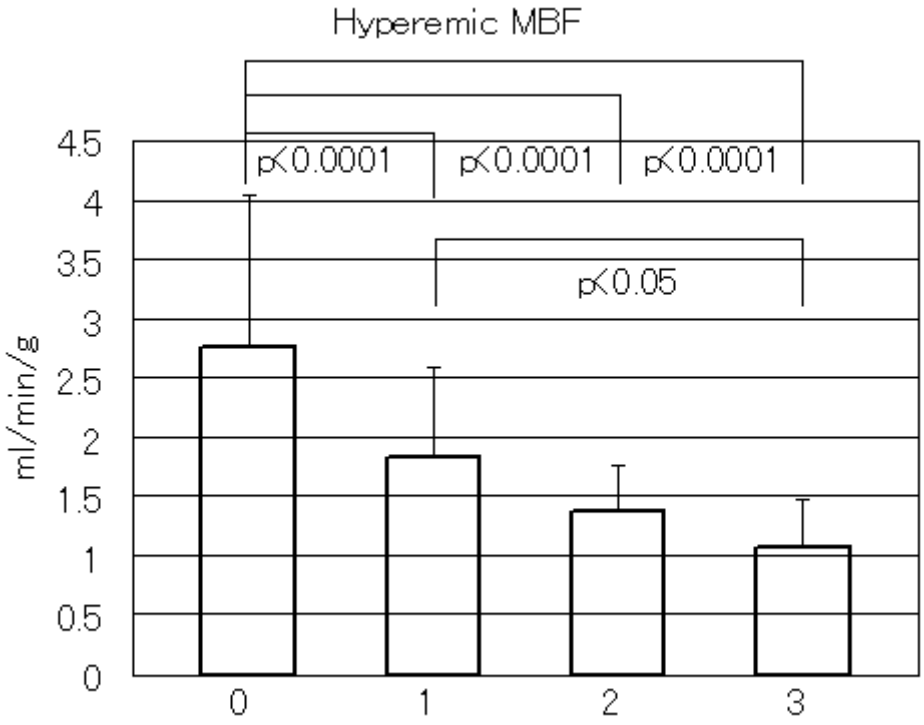
Hyperemic MBF
p<0.0001
p<0.0001
p<0.0001
p<0.05
ml/min/g
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0
1
2
3

Figure 3c

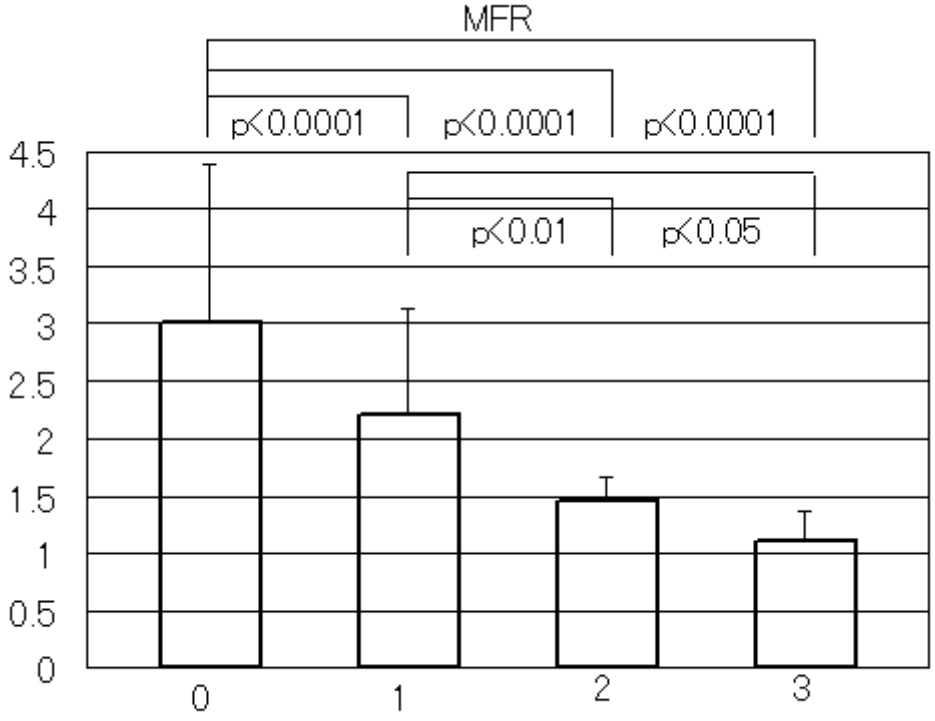

Figure Legends

Figure 1 Division of left ventricle into 13 segments for PET

The 13 segments consist of 6 segments each of basal and apical myocardium and one segment of apex.

Figure 2

A 60-year-old woman with significant coronary stenosis (LAD 90%, Cx 99%). Top row: polar maps of rest MBF and hyperemic MBF and MFR (the color bar on the right: rest MBF and hyperemic MBF and MFR). Bottom row: ^{123}I-BMIPP images of basal short axis (BSA), apical short axis (ASA) and vertical long axis (VLA). ^{123}I-BMIPP image: markedly decreased uptake (score 3), apex of VLA: moderately decreased uptake (score 2), septum and inferior segment of BSA, anteroseptal segment and inferior segment of ASA: slightly decreased uptake (score 1), anterior and inferoseptal segment of ASA. Where ^{123}I-BMIPP uptake is preserved, hyperemic MBF and MFR is preserved. Hyperemic MBF and MFR concordantly decrease with ^{123}I-BMIPP uptake.

Figure 3a Rest MBF for each score

No significant difference was observed in any comparison in the multiple comparison test.

Figure 3b Hyperemic MBF of each score

A significant difference was observed between score 0 and 1, 2 and 3 ($p<0.0001$) and between score1 and 3 ($p<0.05$).

Figure 3c MFR of each score

A significant difference was observed between score 0 and 1, 2 and 3 ($p<0.0001$), between score 1 and 2 ($p<0.01$) and between score1 and 3 ($p<0.05$).